Consumer Healthcare
Products Association

January 10, 2005

Mr. Latroy D. Tinch
Office of Management Programs
Dockets Management Branch, HFA-300
Food and Drug Administration
1061 Fishers Lane
Rockville, MD 20857

RE: Docket No. 81N-0033

Dear Mr. Latroy

This responds to your question concerning the recent submission to Docket No. 81N-0033 in which you indicated that the protocol (Benzocaine Gel Toothache Dose-Response Study: BZ-03-07) being submitted for review under this docket was stamped "confidential."

Although this material was marked "confidential," this material can be released to the public.

Please let me know if you have any questions.

Sincerely,

Douglas W. Bierer, Ph.D.
Vice President – Regulatory & Scientific Affairs

I:\Task Groups\OTCs\Oral Discomfort\Jan 05 ltr to dckt re confidentiality.doc

900 19th Street, NW
Washington, DC 20006
Tel: 202-429-9260
Fax: 202-223-6835
www.chpa-info.org

CONFIDENTIAL

DRAFT

BENZOCAINE GEL TOOTHACHE DOSE-RESPONSE STUDY

BZ-03-07

CHPA Oral Discomfort Task Group
Consumer Healthcare Products Association
900 19th Street, NW, Suite 700
Washington, DC 20006

December 10, 2004

APPROVAL

Protocol BZ-03-07

Benzocaine Gel Toothache Dose –Response Study

The signatures of the Principal Investigator and representatives of the Sponsors below and on the following page constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to all stipulations, clinically and administratively, as detailed in the protocol, including all statements as to confidentiality. It is agreed that the conduct and results of this study will be kept confidential and that the case report forms and other pertinent data will become the property of the CHPA Oral Discomfort Task Group.

It is agreed that the protocol contains all necessary information required to conduct the study as outlined in the protocol, and that the study will not be initiated without the approval of the appropriate Institutional Review Board or Independent Ethics Committee.

It is agreed that all participants in this study will provide written informed consent in accordance with the requirements specified in the U.S. Code of Federal Regulations (21 CFR Parts 50, 56, 312 and the current International Conference on Harmonization Good Clinical Practice Guidelines). All participants will also be informed that their medical records will be kept confidential except for review by representatives of the CHPA Oral Discomfort Task Group, Institutional Review Board or Independent Ethics Committee, and the U.S. Food and Drug Administration and/or an international regulatory authority.

Principal Investigator (Print Name)	Site Number
Principal Investigator (Signature)	Date

Stephen A. Cooper, DMD, PhD
Senior Vice President,
Global Clinical & Medical Affairs
CHPA Oral Discomfort Task Group Representative
Wyeth Consumer Healthcare
5 Giralda Farms
Madison NJ 07940
Tel: (973) 660-5391

Date

Marlene Tietjen
Senior Vice President of Scientific Affairs
CHPA Oral Discomfort Task Group Representative
Del Laboratories, Inc.
178 EAB Plaza, West Tower, 8th Floor
Uniondale NY 11556
Tel: (516) 777-5444

Date

Protocol Date: December 10, 2004

INVESTIGATOR SUMMARY INFORMATION

TITLE: Benzocaine Gel Toothache Dose-Response Study

PROTOCOL NUMBER:	BZ-03-07
PRINCIPAL INVESTIGATOR (S):	Multicenter
CONTRACT RESEARCH ORGANIZATION (CRO):	N/A
MEDICAL MONITOR:	Name: Emanuel Troullos, DMD Phone No.: (973) 660-5137
CLINICAL MONITOR(S):	M. Sudam Pathirana, MS, PhD Phone No.: (973) 660-6686 William E. Cooley, PhD, RAC Phone No.: (513) 522-3797 William O. Thompson, PhD Phone No.: (706) 868-1160
PROJECT MANAGER:	Brenda Wilson Phone No.: (973) 660-5356
CLINICAL RESEARCH ASSOCIATE (S):	Elizabeth de Padova Phone No.: (973) 660-5723
SPONSOR:	CHPA Oral Discomfort Task Group Doug Bierer, PhD Consumer Healthcare Products Association 900 19th Street NW, Suite 700 Washington DC 20006
NAME OF STUDY PRODUCT (STRENGTH):	Benzocaine (10% gel and 20% gel)
IND NO.:	N/A
DATE:	December 10, 2004

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STUDY SYNOPSIS

TITLE:	Benzocaine Gel Toothache Dose-Response Study
STUDY NUMBER:	BZ-03-07
PRINCIPAL INVESTIGATOR (S):	Multicenter
STUDY OBJECTIVES	• To evaluate the efficacy and safety of 10% and 20% benzocaine gel products for the relief of toothache, compared to each other and placebo. • To assess the subject's compliance with the dosing directions in the proposed label.
HYPOTHESES	• 20% benzocaine is significantly more effective than placebo for toothache pain, • 10% benzocaine is significantly more effective than placebo for toothache pain, • 20% benzocaine demonstrates to be more effective than 10% benzocaine for toothache pain*, • At least 75% of the subjects will apply 400 mg or less of the product. *A dose-response will be considered established if a five-percentage-point increase in responders between the 10% and 20% benzocaine treatment groups is observed. Alternatively, since previous studies have suggested that the relative advantage of a 20% concentration of benzocaine to a 10% concentration is most evident among individuals suffering with severe toothache pain, a dose-response will be considered established if the five-percentage-point difference in responders between 10% and 20% benzocaine treatment groups is observed only within the subgroup of subjects presenting with severe toothache pain at baseline.
STUDY DESIGN:	Double-blind, randomized (stratified by baseline pain), single-dose, placebo-controlled, parallel group, out-patient, multi-center

ESTIMATED DURATION OF STUDY:	18 months
DURATION OF EVALUATION:	2 hours
NUMBER OF SUBJECTS:	500 (200 in each of the 10% and 20% benzocaine treatment groups and 100 in the placebo group)
SAMPLE SIZE DETERMINATION:	A sample size of 200 subjects in each benzocaine treatment group and 100 subjects in the placebo group will provide approximately 90% power to detect significant differences between placebo and each of the benzocaine treatment groups, assuming that the response rates are 50% in the benzocaine groups and 30% in the placebo group. A sample size of 200 subjects per benzocaine group will provide approximately 85% power to detect at least a 5% higher response rate in the 20% benzocaine group than in the 10% benzocaine group, assuming that the true response rates (percentage of responders) are 45% with 10% benzocaine and 55% with 20% benzocaine.
DOSAGE:	Application by subjects of an amount of study gel consistent with label directions.
INCLUSION CRITERIA:	a. Males or females at least 12 years of age. b. Presence of spontaneous toothache pain in only one permanent tooth. Toothache pain is due only to an open tooth cavity and only as a result of dental caries, loss of a restoration or tooth fracture. c. To qualify for the study, the subject must have a rating of at least moderate pain on the Dental Pain Scale (DPS) and a score of at least 50 mm on the Visual Analog Scale. To be included in the moderate pain stratum, the subjects must have a rating of moderate pain in the DPS and to be included in the severe pain stratum the subjects must have a rating of severe pain in the DPS. d. Females who are neither pregnant, as verified by a urine-based pregnancy test, nor breast-feeding.

e. Female subjects of childbearing potential and those who are post-menopausal for less than 2 years must be using a medically approved method of contraception (*i.e.,* oral, transdermal or implanted contraceptive devices, intrauterine device, diaphragm, condom, abstinence, or surgical sterility).

f. Subjects must be reliable, cooperative and of adequate intelligence to read and understand the rating scales and other study instructions.

g. Subjects must be able to read, comprehend, and sign the consent form. Minors will provide assent to study participation if age appropriate. Parent/legal guardian must be able to read, comprehend, and sign the informed consent form.

EXCLUSION CRITERIA:

a. Presence of spontaneous toothache pain in a primary tooth. Presence of spontaneous toothache pain in more than one tooth. Presence of an open tooth cavity in a tooth adjacent to the painful tooth with the open tooth cavity.

b. Presence of concomitant oral pain due to any other condition such as: soft-tissue lesions (e.g., aphthous or traumatic ulcer, herpes labialis, acute necrotizing ulcerative gingivitis); or multiple hard-tissue (e.g., carious) lesions; pain due to other surgical procedures, injuries or dental surface sensitivity.

c. Presence of a periodontal abscess as diagnosed from an X-ray or clinical examination of the painful tooth.

d. History of sensitivity or allergy to benzocaine or other local anesthetic agents.

e. Use of any short-acting oral or topical analgesic/ anesthetic product within 2 hours of enrollment or any long-acting Rx or OTC analgesic product within 4 hours of enrollment.

f. Use of an investigational drug or participation in an investigational study within the past 30 days.

g. Previous participation in this study.

h. Member or a relative of the study site staff or sponsor directly involved in the study.

STUDY PARAMETERS:

Baseline:

Dental Pain Scale (DPS):

How much pain do you have at this time? (4-point scale: None (0), Mild (1), Moderate (2), Severe (3))

To be included in the moderate pain category, the subjects must have a DPS rating of moderate pain, and for severe pain category, a DPS rating of severe pain.

Visual Analog Scale (VAS):

"Draw a line on the scale that shows how much pain you have at this time"

"no pain" on the far left end of scale at 0 mm and "pain as bad as it can be" on the far right at 100 mm

Post-baseline:

- **Dental Pain Scale (DPS):** (5-30 min: 5-minute intervals; 30-120 minutes: 10-minute intervals)
- **Dental Pain Relief Scale (DPRS):** How much relief do you have from your starting pain? (5-point scale; no relief (0), a little (1), some (2), a lot (3), complete (4); (5-30 min: 5-minute intervals; 30-120 minutes: 10-minute intervals)
- **Stopwatch:** Onset of Meaningful Relief

SAFETY EVALUATION:

Adverse events will be recorded as they occur.

EFFICACY ANALYSIS:

Primary Efficacy Parameter

- Percentage of responders, where a responder is a subject who experiences an improvement in pain intensity, as exhibited by a pain-score reduction from baseline on the DPS of at least 1 unit, at any two consecutive time points between 5 and 20 minutes.

Secondary Efficacy Parameters

- Time to onset of meaningful relief among *all* subjects
- Duration of effect among *all* subjects (as assessed by the

dental pain scale)

- Sum of pain relief combined with pain intensity difference scores (SPRID) at 30, 60, 90 and 120 minutes
- Pain relief combined with pain intensity difference scores (PRID) at each measurement time
- Time to dropout due to lack of efficacy or time to taking of rescue medication, whichever occurs first.

Other Parameters

- Time to onset of meaningful relief among only the responders in each of the benzocaine groups
- Duration of effect among only the responders in each of the benzocaine groups
- Amount of product applied and percentage of subjects who apply 400 mg or less of the product

STATISTICAL HANDLING OF SUBJECTS WHO DROP OUT OR USE RESCUE MEDICATION

Responder Status: Subjects who drop out (for any reason) or take rescue medication will be considered non-responders unless they have already met the criteria to be considered responders.

Onset of Meaningful Relief: If a subject drops out or takes rescue medication before onset is attained, the subject will be considered censored for analysis purposes. The censoring will be at the end of the scheduled evaluation (120 minutes) if the dropout is due to lack of efficacy (LOE) or if rescue medication was taken; otherwise it will be at the time of the dropout.

Duration of Effect: The difference between offset and onset of effect (see 8.4.2).

- Before onset of effect: Duration will be considered 0 minutes if a subject drops out due to LOE or takes rescue medication. Subjects dropping out due to reasons unrelated to efficacy will not be included in this analysis.
- After onset of effect and before offset: If a subject drops out due to LOE or takes rescue medication, duration will be calculated as the time of the dropout or taking of rescue medication (whichever comes first)

minus the onset time of effect; if a subject drops out due to reasons unrelated to efficacy, the subject will be considered censored for this analysis with a censoring time equal to the dropout time minus the onset time.

Pain scores:

- Dental Pain Scale (DPS): If a subject drops out due to LOE or takes rescue medication, the last score prior to the event or the baseline pain score, whichever is worse, will be carried forward; if a subject drops out due to reasons unrelated to efficacy, the last score will be carried forward.
- Dental Pain Relief Scale (DPRS): A score of "no relief" will be carried forward for subjects dropping out due to LOE or taking rescue medication; the last score will be carried forward for non-efficacy-related dropouts.

STUDY FLOW CHART

	Time Points (min)			
Procedure	**Screening**	**0**	**5-30 (5-min. intervals)**	**30-120 (10-min. intervals)**
Oral Examination[a]	X			
X-ray[a]	X			
Informed Consent	X			
Urine pregnancy test of females	X			
Medical History	X			
Cleanse Tooth	X			
Explain the study procedure	X			
Pain Evaluations:				
Visual Analog Scale	X[b]			
Dental Pain Scale	X[b]		X	X
Dental Pain Relief Scale			X	X
Onset of "meaningful" relief and duration of effect		|→		←|
Randomization: stratified by moderate or severe baseline pain	X			
Weighing of medication tube before dosing	X			
Application of medication by subjects following the label directions		X		
Weighing of tube after dosing			X	
Adverse Event Monitoring/Recording	| →[c]	| →		← |

[a] Initial oral examination and X-ray may be performed as part of routine dental care before the individual is identified as a potential study subject.
[b] within 5 minutes prior to application of study medication.
[c] Monitoring of Serious Adverse Events begins at the signing of Informed Consent.

1.0 INTRODUCTION

Topical benzocaine is currently marketed in 10% and 20% formulations by Wyeth Consumer Healthcare and Del Pharmaceuticals, Inc. for relief of toothache. The ingredient has been assigned monograph status as an external anesthetic/analgesic for the temporary relief of pain due to minor irritation or injury of the mouth and gums, minor dental procedures, dentures, orthodontic appliances, canker sores and teething, sore mouth and sore throat (Notice of Proposed Rulemaking for OTC Oral Health Care Drug Products Amendment to include Relief of Oral Discomfort Products [Docket #81N-0033] published on September 24, 1991 [Federal Register 56(185: 48302-47]). However, the Food and Drug Administration (FDA) concluded that the available data were not adequate to establish the effectiveness of benzocaine for the relief of toothache and did not assign monograph status to benzocaine for this indication.

Wyeth Consumer Healthcare and Del Pharmaceuticals, Inc. submitted the results of eight efficacy studies and one animal safety study to the FDA, which were conducted between 1980-1994 to support the efficacy of the ingredient for this indication. The Agency's response, received in July 1998 noted that "there is some evidence in the data submitted, along with the data contained in the literature, to support the effectiveness of benzocaine-containing gel applied to the tooth cavity for the initial relief of severe and moderate toothache." The Agency requested that an additional study be conducted to determine the efficacy of the agent for this indication, and to assess whether a dose response exists between 10% and 20% benzocaine. In addition, the Agency stipulated that a label be developed that assured safe dosing for temporary relief of toothache pain. The present double-blind, placebo-controlled randomized study will determine the efficacy and the dose-response trend between 10% and 20% benzocaine gel for relieving toothache, and will also help ensure the label directions are adequate in terms of instructing the subjects on the safe use of the product.

2.0 OBJECTIVES AND HYPOTHESES

2.1 OBJECTIVES

The objectives of this study are:

1) To evaluate the efficacy and safety of 10% and 20% benzocaine gel for the relief of toothache, compared to placebo and to each other.

2) To assess the subject's compliance with the dosing directions on the proposed label.

2.2 HYPOTHESES

The statistical hypotheses to be tested are:

1) 20% benzocaine is significantly more effective than placebo for toothache pain as demonstrated by a greater percentage of responders (see Section 8.4.2).

2) 10% benzocaine is significantly more effective than placebo for toothache pain as demonstrated by a greater percentage of responders.

3) 20% benzocaine demonstrates a trend to be more effective than 10% benzocaine for toothache pain (see Section 8.7).

4) At least 75% of the subjects will apply 400 mg or less of the product.

3.0 SUMMARY OF STUDY DESIGN

Approximately five hundred (500) patients presenting to the Emergency Dental Clinics of approximately four dental schools, with moderate or severe pain from an open tooth cavity, and qualified to participate in the study will be enrolled in the study. An objective in recruitment will be to enroll approximately 14% of this population (70 subjects) from minors between the ages of 15-17 and 6% (30 subjects) between the ages of 12-14, respectively. The rest of the enrolled population (400 subjects) will be 18 years and above. Each site will complete the evaluation of approximately 125 subjects.

At the initial pain evaluation, the patients will be assessed for their baseline pain level using the four-category Dental Pain Scale (DPS) followed by the linear Visual Analog Scale (VAS). To qualify for the study, the subject must have at least moderate pain, as confirmed by a rating of moderate pain on the Dental Pain Scale (DPS) and a score of at least 50 mm on the Visual Analog Scale (VAS). Subjects that do not meet this criterion will not be eligible to participate in the study. The VAS scale will be used only at the initial pain evaluation step, to verify the presence of at least moderate pain as rated on the DPS pain measurement at baseline, and to ensure consistency across subjects in the assessment of the minimum pain intensity requirement.

Subjects will be stratified into moderate or severe categories, according to their baseline pain level. To be included in the moderate pain category, the subjects must have a rating of moderate pain in the DPS scale, and for the severe category, a DPS rating of severe pain.

The qualified subjects will be randomized to receive either a single dose of a benzocaine 10% gel formulation, a single dose of a benzocaine 20% gel formulation, or a matching placebo gel under double-blind conditions in this parallel design study.

Subjects will be presented with a product label that will contain directions and a picture of how much product they should apply to their painful tooth and surrounding gum tissue (Appendix I). The weight of the tube (including the cap but not the cut off tip) containing the gel will be measured (in grams) and recorded to the second decimal place by the Investigator or Research Coordinator after cutting off the safety-sealed tip, prior to product application, and then again following product application, employing a Mettler AE-50 Digital Balance. The amount of product used will be equal to the weight of the tube (including the cap but not the cut off tip) prior to product application minus the weight of the tube (including cap) following product application.

Following application of study medication, pain intensity and pain relief will be evaluated using the 4-category Dental Pain Scale (DPS) and the 5-category Dental Pain Relief Scale (DPRS), respectively, at 5-minute intervals from 0-30 minutes and at 10-minute intervals from 30-120 minutes post-dosing (section 6.2.3). The exact time of onset of "meaningful" relief will be recorded by the subject with the use of a stopwatch (section 6.3.4). All adverse events, will be recorded when they occur. The time of rescue medication and time of dropout will be recorded if they occur within the 120-minute evaluation period. At the end of evaluation period, if there were subjects who used 1 gram or more of the product they will be questioned to determine the possible reason for overuse (section 6.2.3).

4.0 SUBJECT POPULATION

4.1 NUMBER OF SUBJECTS

Approximately 500 subjects will be required to complete the study. Approximately 14% of this population (70 subjects) will be minors between the ages of 15 to17 and 6% (30 subjects) between the ages of 12-14, respectively. The rest of the enrolled population (400 subjects) will be 18 years and above. Approximately 200 subjects will be randomized to

each benzocaine treatment group and 100 subjects will be randomized to the placebo group (see Statistical Power - Section 8.1.).

4.2 INCLUSION CRITERIA

Individuals may be included in the study provided they meet all of the following inclusion criteria:

a. Males or females at least 12 years of age.

b. Presence of spontaneous toothache pain in only one permanent tooth. Toothache pain is due only to an open tooth cavity and only as a result of dental caries, loss of a restoration or tooth fracture.

c. To qualify for the study, the subject must have a rating of at least moderate pain on the Dental Pain Scale (DPS) and a score of at least 50 mm on the Visual Analog Scale. To be included in the moderate pain stratum, the subjects must have a rating of moderate pain in the DPS and to be included in the severe pain stratum the subjects must have a rating of severe pain in the DPS.

d. Females who are neither pregnant, as verified by a urine-based pregnancy test, nor breast-feeding.

e. Female subjects of child-bearing potential and those who are post-menopausal for less than 2 years must be using a medically approved method of contraception (*i.e.,* oral, transdermal or implanted contraceptive devices, intrauterine device, diaphragm, condom, abstinence, or surgical sterility).

f. Subjects must be reliable, cooperative and of adequate intelligence to read and understand the rating scales and other study instructions.

g. Subjects must be able to read, comprehend, and sign the consent form. Minors will provide assent to study participation if age appropriate. Parent/legal guardian must be able to read, comprehend, and sign the informed consent form.

4.3 EXCLUSION CRITERIA

Individuals are not eligible for participation in this study if any of the following are noted:

a. Presence of spontaneous toothache pain in a primary tooth. Presence of spontaneous toothache pain in more than one tooth. Presence of an open tooth cavity in a tooth adjacent to the painful tooth with the open tooth cavity.

b. Presence of concomitant oral pain due to any other condition such as: soft-tissue lesions (e.g., aphthous or traumatic ulcer, herpes labialis, acute necrotizing ulcerative gingivitis); or multiple hard-tissue (e.g., carious) lesions; pain due to other surgical procedures, injuries or dental surface sensitivity.

c. Presence of a periodontal abscess as diagnosed from an X-ray or clinical examination of the painful tooth.

d. History of sensitivity or allergy to benzocaine or other local anesthetic agents.

e. Use of any short-acting oral or topical analgesic/anesthetic product within 2 hours of enrollment or any long-acting Rx or OTC analgesic product within 4 hours of enrollment.

f. Use of an investigational drug or participation in an investigational study within the past 30 days.

g. Previous participation in this study.

h. Member or a relative of the study site staff or sponsor directly involved in the study.

5.0 CLINICAL SUPPLIES

5.1 STUDY PRODUCT AND DOSAGE

The Sponsor will supply the 10% and 20% benzocaine gel products, matching placebo gel, and the label directions for dosing.

5.2 PACKAGING AND LABELING

Study medication will be manufactured and packaged in 0.42 oz (12 g) tubes at Del Pharmaceuticals, Inc. and sent to Wyeth Consumer Healthcare for double-blind labeling and packaging into boxes prior to distribution to each study site.

A sealed disclosure on each label containing the identification of the package contents may be opened only in an emergency if medically necessary. Procedures to be followed, notification responsibilities, and regulatory requirements are detailed in Section 7.4.5 Breaking the Blind.

The treatment kit (box) for each subject will contain a study medication tube labeled with a single-panel label (see below). The box containing the tube will be labeled with a three-panel double-blind label.

Gel tube label:

Study: BZ-03-07 Subject #: XXXXX
Dr.: Subject Initials: _____
Date Dispensed: ___/___/___
Contents: 0.42 oz of Gel
Directions: Apply as directed
Store between 20°C to 25°C (68°F to 77°F)
Caution: Experimental Drug-Limited by Federal Law to Investigational Use
Manufactured by Del Pharmaceuticals, Inc.,
Labeled by Wyeth Consumer Healthcare for the
CHPA Oral Discomfort Task Group,
Washington, DC 20006

Outer box three-panel double-blind label:

Panel 1 (container panel):

Study: BZ-03-07 Subject # XXXXX
Dr.: Subject Initials: _____
Contents: 1 Tube
Store between 20°C to 25°C (68°F to 77°F)
Caution: Experimental Drug-Limited by
Federal Law to Investigational Use
Manufactured by Del Pharmaceuticals, Inc.,
Labeled by Wyeth Consumer Healthcare for
the
CHPA Oral Discomfort Task Group,
Washington DC 20006

Panel 2

Study: BZ-03-07 Subject # XXXXX
Dr.: Subject Initials: _____
Date Dispensed: ____/____/____
Caution: Experimental Drug-Limited by
Federal Law to Investigational Use
Attach this portion of the label to
the case report form
Manufactured by Del Pharmaceuticals, Inc.,
Labeled by Wyeth Consumer Healthcare for
the
CHPA Oral Discomfort Task Group
Washington DC 20006

Panel 3

DRUG INFORMATION INSIDE
UNBLIND ONLY
IN CASE OF EMERGENCY

TO UNBLIND
TEAR COVER AT PERFORATION
AND SCRATCH OFF

Panel 1 is affixed to the box and a tear-off section (panels 2 and 3) will be affixed to the subject's Case Report Form. Panel 3 is the scratch-off, double-blind disclosure panel.

The Investigator should only unveil the scratch-off double-blind disclosure panel in the event of emergency or if medically necessary. Every effort should be made to discuss the decision to break the blind with the CHPA Oral Discomfort Task Group monitors in advance. In the event that the sealed disclosure panel is opened, the Investigator must notify the sponsor and the IRB immediately and the subject must be discontinued from this study (See Section 7.4.5 for additional information regarding breaking the blind).

5.3 ASSIGNMENT OF STUDY PRODUCT

Treatment assignments will be determined by a computer-generated randomization schedule and maintained by personnel in the Biostatistics and Data Management Division of Wyeth Consumer Healthcare, designated by the CHPA Oral Discomfort Task Group. Subjects will be randomly allocated to the three treatment groups (benzocaine 10% gel, benzocaine 20% gel or placebo gel) in a 2:2:1 ratio. Following completion of the baseline dental pain measurements (see Sections 6.3.1 and 6.3.2), the subjects will be stratified into one of two categories based on their baseline pain intensity (DPS) scores as follows:

ASSIGNMENT OF RANDOMIZATION NUMBERS

Moderate	Severe
10000 series beginning with 10101	20000 series beginning with 20101

Study medication from each stratum may be shipped to the sites on an as-needed basis, in sequential blocks.

5.4 ADMINISTRATION OF STUDY PRODUCT AND DURATION OF EVALUATION

Prior to baseline pain evaluation and product application, the Investigator or his designee will gently clean the area around the open tooth cavity with gauze and/or a gloved finger, if necessary. No dental instruments, water or air will be used to cleanse the area.

After the completion of baseline pain evaluation, the subjects will be given a card that contains the label directions for dosing, including a picture of how much gel they should apply to their painful tooth and surrounding gum tissue (Appendix I), along with the study medication tube (with the tip cut off), and asked to self-apply an amount of the study medication following the label directions. The weight of the medication tube (with cap) will be measured and recorded before and after use. The duration of the evaluation period will be 120 minutes following application of the study medication.

5.5 STUDY PRODUCT ACCOUNTABILITY

5.5.1 Storage

All materials for this study must be stored in an area free from environmental extremes and with restricted access. A CHPA Oral Discomfort Task Group representative will inspect the study product storage area and discuss the study product accountability system with the Principal Investigator before study initiation.

5.5.2 Study Product Inventory

Upon receipt at each study site, the carton containing the study product supplies will be stored unopened in the study product storage room. At the study initiation, the Principal Investigator or an appropriate designee, and a representative of the CHPA Oral Discomfort Task Group will conduct an inventory and complete the study product inventory record. The original will be sent to the CHPA Oral Discomfort Task Group representative and the Principal Investigator will retain a copy. Any interim shipments will be inventoried by the Principal Investigator or his/her designee, and if possible, a representative of the CHPA Oral Discomfort Task Group. For all interim shipments, a study product inventory record will be completed. The original will be returned to the CHPA Oral Discomfort Task Group representative and the Principal Investigator will retain a copy.

The Principal Investigator or an appropriate designee at each site, upon dispensing the study product, must record the information on a study product dispensing/return log. For accounting purposes and assessing subject compliance, a representative of the CHPA Oral Discomfort Task Group will review the study product dispensing/return log, inventory the study product, and inspect the storage facility at appropriate time intervals throughout the clinical investigation, depending on the length of the study. The Principal Investigator must account for any significant discrepancy and/or deficiency.

5.5.3 Return of Study Supplies

All investigational study products shipped for this clinical trial must be returned to the Sponsor at the termination of the study. At the conclusion of the study, each Principal Investigator or an appropriate designee at each site, and a representative of the CHPA Oral Discomfort Task Group will inventory all used and unused investigational study product. The study product inventory record for returned study products will then be completed. The CHPA Oral Discomfort Task Group will retain the original, and the Investigator will retain a copy for his/her files. All used investigational study product (empty containers), as well as all unused study product and dosing direction cards will then be returned to:

CHPA Oral Discomfort Task Group
C/O Wyeth Consumer Healthcare
Experimental Packaging
1211 Sherwood Avenue
Richmond VA 23220
Attention: Returned Study Supplies
Protocol No. BZ-03-07
(804) 257-2905

Upon receipt at WCH Experimental Packaging, Richmond, VA, a letter acknowledging the receipt of returned materials and a copy of the packing slip will be sent to the Clinical Monitor.

6.0 STUDY PROCEDURES

6.1 STUDY CONDITIONS

a. Only subjects who meet all entry criteria and provide written informed consent may participate in the trial. A parent/guardian who agrees to have his/her child participate in the study, based on reading and understanding of the informed

consent documents, will provide written informed consent and the child will provide assent (if age appropriate) before participating in the study.

b. Patients presenting to the Emergency Clinic of the dental school with a primary complaint of at least moderate pain from an open tooth cavity in only one permanent tooth will be screened to determine if they meet study entry criteria.

c. Initial evaluation of patients to identify the potential study subjects will be conducted by the Investigator, or an emergency clinic dentist, designated by the Investigator. This will include a medical history and an X-ray of the affected tooth.

d. If a potential study subject is identified during this initial evaluation by a designee, the candidate subject and his/her medical information will be referred to the Investigator or the Coordinator.

e. If the Investigator determines the potential subject may be a candidate for the study, the informed consent process will be initiated.

f. History of menarche will be obtained for female subjects below 18 years of age. A urine pregnancy test will be performed on female subjects of child-bearing potential.

g. The Investigator or Coordinator will obtain the medical history, and information on medication use, particularly, the use of topical and systemic analgesics, and review the rest of the inclusion/exclusion criteria to determine if the subject is eligible to participate in the study.

h. If necessary, the tooth to be treated will be gently cleaned by removing debris with gauze and/or a gloved finger by the Investigator or Coordinator. No dental instruments, water or air will be applied to the tooth.

i. After cleaning the affected tooth (if needed) and just prior to dosing with study medication, the investigator or coordinator will explain and administer the Dental Pain Scale (DPS) to the subject, followed by the Visual Analog Scale (VAS), to assess the baseline pain level. To qualify for the study, the subject must have a rating of at least moderate pain on the Dental Pain Scale (DPS) and a score of at least 50 mm on the Visual Analog Scale. Subjects that do not meet this criterion will not be eligible to participate in the study. The VAS scale will be used only at the initial pain evaluation step, to verify the presence of at least moderate pain as rated on the DPS pain measurement at baseline, and to ensure consistency across subjects in the assessment of the minimum pain intensity requirement.

j. Qualified subjects will be stratified into moderate or severe categories, according to their baseline pain level. To be included in the moderate pain category, the subjects must have a rating of moderate pain in the DPS scale, and for the severe category, a rating of severe pain in the DPS scale.

k. If the subject qualifies, the investigator or coordinator will assign the next consecutive subject number and explain the study procedure to the subject.

l. The Investigator or Coordinator will cut off the sealed tip of the tube at the score mark on the medication tube, close the cap and weigh before product application. Weight of the treatment tube including the cap (without the cut tip) will be measured (in grams) and recorded to the second decimal place.

m. The subjects will be given a card that contains the label directions and a picture of how much gel they should apply to their painful tooth and surrounding gum tissue.

n. The subjects will self-apply an amount of the study gel, consistent with the picture on the label directions card, to the affected tooth and surrounding gum tissue. Subjects will be allowed to look in a mirror to correctly locate the affected tooth, if needed.

o. As the subject begins to apply the study gel, (t = 0 min), the Investigator or Coordinator will start the stopwatch, then hand it to the subject and instruct the subject to press and stop the watch at the onset of meaningful relief.

p. Following study gel application, the subject will return the gel tube and cap to the Coordinator. The Coordinator will measure and record the weight of the treatment tube (including the cap) to the second decimal.

q. Investigator or Coordinator will request subjects to rate the intensity of their toothache pain on the DPS (section 6.3.1) at 5-minute intervals from 5 through 30 minutes and at 10-minute intervals from 30-120 minutes post-dosing. They will also rate the relief of their starting toothache pain at the same time points on the Dental Pain Relief Scale (section 6.3.3).

r. During the 120-minute evaluation period, the subjects will remain seated in the designated evaluation room.

s. Subjects are not allowed to eat, drink or smoke during the 120-minute evaluation period.

t. Investigator or Coordinator will conduct evaluations on only one subject at any given time and will remain with the subject from enrollment to the completion of evaluation period.

u. Adverse events, if any, will be recorded in the subject's Case Report Form when they occur.

v. If a subject does not experience pain relief, or the analgesic effect of the product dissipates before 120 minutes, the subject will be allowed to ingest rescue medication upon request (section 6.6). An assessment of pain intensity and pain relief will be completed at the time rescue medication is taken. No further evaluations are performed after rescue medication is taken.

w. At the conclusion of the evaluation period (120 minutes), if there were subjects who used 1 gram or more of the product, they will be questioned to determine the possible reason for overuse (section 6.2.3).

x. At the completion of all assessments, subjects will be referred to the appropriate clinic for treatment.

6.2 SCHEDULE OF ASSESSMENTS

6.2.1 Screening Assessments

The Investigator or his/her designee in each emergency clinic will examine the subject in order to determine his/her eligibility. The Investigator (or designee) will enter the pertinent historical information (including any medication and alcohol use) and clinical findings in the appropriate sections of the subject's Case Report Form. A Subject Screening and Enrollment Record will be maintained and all subjects who provide signed Informed Consent Forms for entry into the study will be recorded. The specific reasons given for subjects who are excluded from the study will also be recorded. All subjects who meet the entrance criteria will provide written informed consent before participating in the study. A parent/guardian who agrees to have his/her child participate in the study, based on reading and understanding the informed consent documentation, will provide written informed consent and the child will provide assent (if age appropriate) before participating in the study.

6.2.2 Baseline Assessments

After cleaning the affected tooth (if needed) and just prior to dosing with study medication, the Investigator or Coordinator will explain and administer the Dental Pain Scale (DPS) to the subject, followed by the Visual Analog Scale (VAS), to assess the baseline pain level. To

qualify for the study, the subject must have a rating of at least moderate pain on the Dental Pain Scale (DPS) and a score of at least 50 mm on the Visual Analog Scale. Subjects that do not meet this criterion will not be eligible to participate in the study (Sections 6.3.1 and 6.3.2). The VAS scale will be used only at the initial pain evaluation step, to verify the presence of at least moderate pain as rated on the DPS pain measurement at baseline, and to ensure consistency across subjects in the assessment of the minimum pain intensity requirement.

To be included in the moderate pain category, the subjects must have a rating of moderate pain in the DPS scale, and for the severe category, a rating of severe pain in the DPS scale (Section 6.3.1).

Upon completion of the baseline Dental Pain Scales, subjects will apply an amount of study medication onto the affected tooth and the gingiva around the tooth, according to label instructions on the card they are given (Appendix I). The amount of product actually applied will be measured by weighing the tube (with the cap) on a Mettler AE-50 Digital Balance both before and after application.

6.2.3 Post-Baseline Assessments

a. Subjects will rate the intensity of their toothache pain on the Dental Pain Scale at 5-minute intervals from 5 through 30 minutes and at 10-minute intervals from 30 through 120 minutes post-dosing. They will also rate the relief of their toothache pain relative to the baseline, at the same time points on the Dental Pain Relief Scale (section 6.3.3).

b. Subjects will evaluate the Onset of "Meaningful" Relief by depressing a stopwatch when they first experience relief that they perceive is meaningful to them.

c. At the conclusion of the evaluation period (120 minutes), if there were subjects who used 1 gram or more of the product, they will be asked the question:

> "In this study, you used more product than what was shown in the directions card. What led you to dispense that amount of product?"

d. Adverse events, if any, will be recorded when they occur.

6.3 EFFICACY ASSESSMENTS

6.3.1 Dental Pain Scale (DPS)

The following 4-category scale will be used to rate the intensity of baseline pain in response to the query:

"How much pain do you have at this time?

None; Mild; Moderate; Severe"

Responses in this scale will be assigned values from 0 (None) to 3 (Severe).

To qualify for the study, the subject must have a rating of at least moderate pain on the Dental Pain Scale (DPS) and a score of at least 50 mm on the Visual Analog Scale (section 6.3.2).

To be included in the moderate pain category, the subjects must have a DPS rating of Moderate, and severe category a DPS rating of Severe.

The 4-category DPS will be completed again 5 minutes after application of the study medication and then at 5-minute intervals up to 30 minutes post- dosing, and at 10-minute intervals from 30 through 120 minutes post-dosing, to evaluate pain intensity in response to the question:

"How much pain do you have at this time?

None, Mild, Moderate or Severe"

Responses in this scale will be assigned values from 0 (None) to 4 (Severe).

6.3.2 Visual Analog Scale (VAS)

The VAS will be used to evaluate the intensity of baseline pain in response to:

"Draw a line on the scale that shows how much pain you have at this time"

"no pain" on the far left end of scale at 0 mm and "pain as bad as it can be" on the far right at 100 mm

To qualify for the study, the subject must have a rating of at least moderate pain on the Dental Pain Scale (DPS) and a score of at least 50 mm on the Visual Analog Scale.

6.6 RESCUE MEDICATION

Subjects who do not experience pain relief or whose pain returns any time before the 120-minute time point will be allowed to ingest the rescue analgesics ibuprofen up to 400 mg or acetaminophen up to 1000 mg. Dosing for minor subjects will be determined by the investigator. An assessment of pain intensity and pain relief will be completed at the time rescue medication is taken. No further evaluations are performed after rescue medication is taken. Subjects are required to remain in the study center for 120 minutes.

The use of rescue medication will be recorded in the appropriate section of the Case Report Form. The date, time, name of rescue medication taken, and reasons for use will be recorded.

6.7 STUDY PARTICIPANT DISCONTINUATION

A subject will be considered discontinued from the study at any time under the following circumstances:

a. Any subject who violates any condition of the entrance criteria after having been entered into the study;

b. Any subject who develops a confounding concomitant illness (as determined by the subject, Research Coordinator or Investigator), serious adverse event, or a hypersensitivity to the study product;

c. Any subject who becomes uncooperative, does not adhere to the requirements of the study protocol, or refuses to complete the study;

d. Any subject who requires any concomitant medication (except for ibuprofen up to 400 mg or acetaminophen up to 1000 mg, age-appropriate dosing determined by the Investigator) that could confound the evaluation of study drug during the 120- minute evaluation.

Additional coded study product will be provided to the study site for replacement subjects. Should a subject discontinue, he/she will be replaced by the next available subject number. Subjects who discontinue due to an adverse event will not be replaced. If possible, the reason(s) why a subject has been discontinued from the study should be recorded in the appropriate section of the case report form. All discontinued subjects will be included in the safety and primary (intent-to-treat) efficacy analyses if they have taken study medication and their follow-up data are available.

6.3.3 Dental Pain Relief Scale

The following 5-category scale will be completed after the DPS assessment at 5 minutes after application of the study medication and then at 5-minute intervals up to 30 minutes post-dosing, and at 10-minute intervals from 30 through 120 minutes post-dosing, to evaluate pain relief in response to the question:

"How much relief do you have from your starting pain?

No relief; A Little; Some; A Lot; Complete"

Responses in this scale will be assigned values from 0 (no relief) to 4 (complete relief).

6.3.4 Onset of Meaningful Relief (Stopwatch Timing)

When the subject begins to administer study medication, the Study Coordinator will start a stopwatch and will cover the time display on the stopwatch. In an effort to determine the exact moment that the subject begins to obtain meaningful pain relief, the subject will be instructed as follows:

"Depress the stopwatch when you have meaningful pain relief, that is, when the relief from the pain is meaningful to you."

The elapsed time will be recorded in the Case Report Form. The evaluation of Onset of Meaningful Relief is described in Section 8.4.2.

6.4 SAFETY ASSESSMENTS

Adverse events will be monitored and recorded when they occur. The recording period for a serious adverse event starts at the time the subject or parent/guardian signs the informed consent through 15 days after the dose of study medication. The recording period for a non-serious adverse event starts at the time the subject takes the first dose of study product (see 7.4.4) and will continue through 15 days after the dose. Only the Principal Investigator will determine the relationship of each adverse event to study product.

6.5 CONCOMITANT MEDICATION

No other medications expected to confound the evaluation of the study drug will be allowed during the course of the study. All concomitant medications used by the subject during the study will be recorded in the subject's Case Report Form.

6.8 FINAL EXAMINATION

Subjects will be referred to the appropriate clinic for definitive treatment at the end of their scheduled 120-minute participation in the study.

7.0 SAFETY

7.1 SUBJECT EXAMINATIONS

To ensure the safety and well being of each subject entered into the study, the subject must first be examined by the Principal Investigator or a designated emergency clinic dentist and medically cleared to participate as required by the protocol. Each subject will be observed for adverse events and will be required to report to the Investigator any adverse events that develop during the course of the study. If at any time during the study, the subject has a serious adverse event or abnormality, the subject must be withdrawn from the study and appropriate care should be initiated.

7.2 SUBJECT SAFETY INFORMATION

In accordance with the regulatory requirements regarding informed consent (21 CFR Part 50, Protection of Human Subjects), the subject or the subject's parent/guardian will receive a copy of the Informed Consent Form when discharged from the clinic. The Informed Consent Form will include the information needed to contact the Principal Investigator, along with a description of the study product the subject may have received.

7.3 AVAILABILITY OF INVESTIGATOR

Either the Principal Investigator or an appropriate designee at each site will be available to the subject at all times during the study. Names and phone numbers of the Principal Investigator and/or appropriate designee will be listed in the Informed Consent Form.

7.4 ADVERSE EVENTS

7.4.1 Definitions

7.4.1.1 Adverse Events

An adverse event is defined as any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a human being administered a CHPA Oral Discomfort Task Group product or in a CHPA Oral

Discomfort Task Group clinical study. The event does not need to be causally related to the CHPA Oral Discomfort Task Group product or CHPA Oral Discomfort Task Group clinical study. This includes:

- Any clinically significant worsening of a pre-existing condition. (A pre-existing condition is a clinical condition [including a condition being treated] that is diagnosed or identified before the subject signs the informed consent form and that is documented as part of the subject's medical history.);

- An adverse event occurring from overdose (overdose for this study is defined as an amount equal or greater than 15 mg of benzocaine per kilogram of body weight, which is equal to 75 mg of 20% benzocaine gel, per kilogram of body weight[1]; or 3750 mg of 20% benzocaine gel for an individual weighing 50 kg) of a CHPA Oral Discomfort Task Group product, whether accidental or intentional;

- An adverse event occurring from abuse (*e.g.*, use for non-clinical reasons) of a CHPA Oral Discomfort Task Group product;

- An adverse event that has been associated with the discontinuation of the use of a CHPA Oral Discomfort Task Group product.

A medical or dental procedure is not classified as an adverse event, but the reason leading to the procedure may be an adverse event.

For this CHPA Oral Discomfort Task Group clinical trial, the definition of an adverse event is any unintended change in pathology or in anatomic, metabolic, or physiologic functioning occurring in a person administered a CHPA Oral Discomfort Task Group product (including placebo) when participating as a subject in a CHPA Oral Discomfort Task Group clinical study. These changes are typically reflected by physical signs, reported symptoms, or laboratory data. However, a pre-existing condition that does not change in severity, as well as changes associated with normal growth and development not varying in frequency or magnitude from that normally anticipated clinically, are not considered adverse events (*e.g.*, onset of menstruation occurring at physiologically appropriate time or normal post-surgical sequelae). This definition includes events occurring during a clinical trial or within 15 days after the administration of study product. Furthermore, any concomitant illness that a subject develops during the study must be recorded on the adverse event case report form page. Whenever possible, a concomitant illness will be recorded as a diagnosis rather than a series of symptoms.

A detailed series of symptoms can be recorded in the comment section following the adverse events page.

If there is any doubt whether the information constitutes an adverse event, the information will be treated as an adverse event.

7.4.1.2 Adverse Event Severity

The following definitions will be used for grading severity of adverse events:

Mild - Either asymptomatic, or subject is aware of the sign, symptom or event, but it is easily tolerated.

Moderate - Discomfort enough to cause interference with usual activity and may warrant intervention.

Severe - Incapacitating with inability to do usual activities.

7.4.1.3 Adverse Event Causality

When assessing the likelihood that an adverse event is causally related to an investigational product or protocol, the following parameters will be considered:

- Temporal relationship between the investigational product/protocol and the adverse event;
- Biologic plausibility of relationship;
- Subject's underlying clinical state or concomitant agents/therapies;
- Where applicable, does the event abate on discontinuation of the investigational product (i.e., dechallenge);
- Where applicable, does the event reappear on repeat exposure to the investigational product (i.e., rechallenge).

The following definitions will be used to assess relatedness of an adverse event:

Definitely Related – Event can be fully attributable to administration of the investigational product.

Probably Related – Event is most likely to be explained by administration of the investigational product, rather than the subject's clinical state or other agents/therapies.

Possibly Related – Event is as likely to be explained by administration of the investigational product as by the subject's clinical state or other agents/therapies.

Probably Not Related – Event is most likely to be explained by the subject's clinical state or other agents/therapies, rather than the investigational product.

Definitely Not Related – Event can be fully explained by the subject's clinical state or other agents/therapies, rather than investigational product.

7.4.1.4 Serious Adverse Event

A serious adverse event is any adverse event that:

- Results in death;
- Is life threatening (i.e., immediate risk of death as the event occurred. A life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal);
- Results in persistent or significant disability or incapacity (i.e., a substantial, persistent disruption in a subject's ability to conduct normal life functions);
- Requires hospitalization or prolongation of an existing hospitalization (N.B., hospitalization is only to be considered as an overnight admission. A hospitalization planned before the start of a study for a pre-existing condition that has not worsened does not constitute a serious adverse event, e.g., elective hospitalization for a total knee replacement due to pre-existing condition of osteoarthritis of the knee that has not worsened during the study.);
- Results in cancer;
- Results in a congenital anomaly or birth defect.

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event(s) may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse. If there is any doubt whether the adverse event constitutes a serious adverse event, the information will be treated as a serious adverse event.

7.4.2 Reporting of Adverse Events

Any **serious adverse event**, regardless of causal relationship, must be reported immediately to a CHPA Oral Discomfort Task Group monitor as listed in the front of this protocol (*i.e.*, no later than 24 hours after the Principal Investigator becomes aware of the serious adverse event) by faxing a completed CHPA Oral Discomfort Task Group Adverse Event Record Form and then confirming by telephone that the fax was received. Compliance with this time requirement is essential so that CHPA Oral Discomfort Task Group may comply with its regulatory obligations. If the CHPA Oral Discomfort Task Group monitors listed in the beginning of this protocol are not available, then the Investigator must contact the following within 24 hours after learning of a serious adverse event:

Emanuel Troullos, DMD
CHPA Oral Discomfort Task Group
Wyeth Consumer Healthcare
5 Giralda Farms
Madison NJ 07940
(973) 660-5137 (day)
(973) 204-9051 (night)

Follow-up information relating to a serious adverse event must be reported to the CHPA Oral Discomfort Task Group monitor within 24 hours of receipt by the Principal Investigator by faxing a completed CHPA Oral Discomfort Task Group Adverse Event Record Form to CHPA Oral Discomfort Task Group and confirming by telephone that the fax was received. The subject will be observed and monitored carefully until the condition resolves, stabilizes, or its cause is identified. The Principal Investigator will also promptly notify the appropriate Institutional Review Board about the serious adverse event.

7.4.3 Other Reportable Events

The following events will be recorded and reported in the same time frame and following the same process as for serious adverse events:

- Overdose or abuse (i.e., use for nonclinical reasons) of the study product with or without adverse events (overdose for this study is defined as an amount equal or greater than 15 mg of benzocaine per kilogram of body weight, which is equal to 75 mg of 20% benzocaine gel, per kilogram of body weight1; or 3750 mg of 20% benzocaine gel for an individual weighing 50 kg);

- Inadvertent or accidental exposure to the study product with or without an adverse event.

7.4.4 Adverse Event Recording and Reporting

All adverse events, whether serious or not, will be recorded on source documents and case report forms. The recording period for a serious adverse event starts at the time the subject signs the informed consent. This includes events that emerge during screening. The recording period for a non-serious adverse event starts at the time the subject takes the first dose of study product. The recording period for both serious and non-serious adverse events lasts through 15 days after the subject's last administration of study product, regardless of relationship to the study product or protocol. The Principal Investigator must follow up as medically necessary on all adverse events, serious adverse events, and other reportable events until the event has subsided or values have returned to baseline, or in the case of permanent impairment, until the condition stabilizes.

For serious adverse events, the Principal Investigator will provide all documentation pertaining to the event (*e.g.,* additional laboratory tests, consultation reports, discharge summaries, postmortem reports, etc.) to the CHPA Oral Discomfort Task Group monitor in a timely manner. Reports relative to the subject's course must be submitted to CHPA Oral Discomfort Task Group until the event has subsided or, in the case or permanent impairment, until the condition stabilizes.

Information about all adverse events, serious and non-serious, including the event's severity, start and stop times/dates, chronicity, relatedness to study product, and any actions taken, must be recorded on the appropriate case report forms. The information recorded will be based on the signs and symptoms detected during the physical examination and clinical

evaluation of the subject as well as information recorded in the subject's diary, when applicable.

7.4.5 Breaking the Blind

In the event of a medical emergency that necessitates breaking the code, the sealed disclosure on the label containing emergency identification of the package contents may be opened. This disclosure will only be broken by the Investigator in the event of an emergency for which knowledge of the subject's double-blind investigational product will have a direct impact on treatment decisions. Every effort will be made to discuss the decision to break the blind with the CHPA Oral Discomfort Task Group monitor in advance.

When the blind is broken, the Investigator will notify the Sponsor's Clinical/Medical Monitor immediately and document the reason and date of the unblinding. The event will also be recorded on the case report form and in the source document. Additionally, the Investigator will submit a written explanation to the Sponsor describing the event within 5 business days.

8.0 STATISTICAL METHODS AND DATA HANDLING

Wyeth Consumer Healthcare and William O. Thompson, PhD, Professor Emeritus and Director of Biostatistics, Medical College of Georgia, the statistical consultant to Del Pharmaceuticals, Inc, will perform the statistical analyses. All computations will be performed using SAS® version 8.2 (SAS Institute, Cary, NC). Statistically significant treatment differences will be declared if the probability of random occurrence among or between the treatment groups, p, is ≤ 0.05. Treatment differences will be declared marginally significant if $0.05 < p \leq 0.10$. Adjustments for multiple comparisons are described in Section 8.6. All between-group tests will be two sided. No interim analyses are planned.

8.1 STATISTICAL POWER

A sample size of 200 subjects per benzocaine treatment group and 100 subjects in the placebo group will provide about 90% power to detect significant differences between each of the benzocaine groups versus placebo, assuming that the response rates are 50% in a given benzocaine group and 30% in the placebo group (Previous studies conducted by Del

Laboratories for treatment of benzocaine in toothache pain had a placebo response rate of about 30%).

A sample size of 200 subjects per benzocaine group will provide approximately 85% power to detect at least a 5% higher response rate in the benzocaine 20% group than in the 10% group, assuming that the true rates are 45% with 10% benzocaine and 55% with 20% benzocaine.

8.2 DEMOGRAPHIC DATA AND BASELINE COMPARABILITY

A series of statistical tests will be performed to assess the treatment group comparability at baseline. Variables with continuous distributions (i.e., age and weight) will be analyzed via analysis of variance. Categorical data (e.g. sex, race) will be analyzed via the Cochran-Mantel-Haenszel (CMH) test, taking order into account via MODRIDIT scores (i.e., percentile ranks) when appropriate. Baseline pain severity will be analyzed by the Cochran-Mantel-Haenszel test (see Section 8.5. for details of the statistical models).

8.3 EFFICACY EVALUATIONS

8.3.1 Primary Efficacy Parameters

The primary efficacy parameter is the percentage of responders, as defined in section 8.4.2.

8.3.2 Secondary Efficacy Parameters

- Onset time to meaningful relief among all subjects
- Duration of effect among all subjects
- Sum of pain relief combined with pain intensity difference scores (SPRID) over 30, 60, 90 and 120 minutes
- Pain relief combined with pain intensity difference scores (PRID) at each measurement time
- Time to dropping out of the study due to lack of efficacy or taking of rescue medication, whichever comes first

Section 8.4.2 defines the derived parameters.

8.3.3 Other Parameters:

- Onset time to meaningful relief among just the responders in the benzocaine groups
- Duration of effect among just the responders in the benzocaine groups
- Amount of study medication applied and the percentage of subjects who apply no more than 400 mg of the product. (These variables are of primary interest for the pooled treatment groups since the type of gel, active or placebo, is blinded.)

8.4 DATA ADJUSTMENTS AND DERIVED ENDPOINTS

8.4.1 Time Windows

Efficacy assessments will be completed every 5 minutes up to 30 minutes and every 10 minutes thereafter up to 2 hours post-dose, and analyses will be done corresponding to these scheduled time points. However, the assessments recorded in the case report forms at those scheduled times will not necessarily be used in the analysis for that time point. Instead, an analysis that more accurately reflects the **actual** times of the assessments will be performed. Time windows will be created for each analyzed time point. For the 5-30 minute time points, the window widths are **± 2 minutes**. For the subsequent time points, the window widths are **± 4 minutes**. All relief and pain intensity scores for each subject will be assigned to analyzed time points according to these windows. The assignment rules will be as follows:

- Any assessment completed more than a minute after a subject takes rescue medication will be ignored. (One minute is allowed in case the subject does an evaluation pertaining to the time of rescue medication, but actually records the values immediately after taking the rescue medication.) Remaining efficacy scores subsequent to the time rescue medication is taken will be extrapolated as described below.
- If an assessment was performed within a time point window, the corresponding value will be assigned to that time point (e.g., an assessment performed anywhere between 8 and 12 minutes, regardless of when it was scheduled, will be assigned to the 10-minute time point). If more than one value falls within a window, a simple average of the values will be used.
- If a particular time point has no value within its window, then a value will be assigned by either interpolation or extrapolation. If an assessment is available after the time point window, then interpolation will be done by calculating the weighted average of the values immediately preceding and subsequent to the time

point window, with weights inversely proportional to the duration between the analyzed time point and the actual time.

For example, suppose an assessment is done at 45 minutes, followed by the next one at 56 minutes. Since no assessment falls within the 50-minute time point window (46-54 minutes), a weighted average of the values at 45 and 56 minutes would be assigned to it, with weights equal to 6/11 for the value at 45 minutes and 5/11 for the value at 56 minutes.

If the 5-minute window is empty and no preceding post-dosing score is available, the baseline DPS value will serve as the preceding DPS value and 0 (no relief) will serve as the preceding DPRS value.

- If a window is empty and no subsequent scores are available, a value will be assigned to the empty window via extrapolation. The extrapolated value will depend on whether rescue medication is taken during or before the particular time point's window. If rescue medication has been taken, the preceding or baseline value, whichever is worse, will be assigned for the DPS scale, and a score of 0 (no relief) will be assigned for the DPRS scale. If no rescue medication is taken, the preceding score will be assigned.

8.4.2 Derived Endpoints

All derived endpoints will be computed after missing values are imputed, as described in the previous section.

- Responders

  A responder is a subject who experiences an improvement in pain intensity, as exhibited by a pain score reduction on the Dental Pain Scale from baseline of at least 1 unit for two consecutive assessments anytime between the 5 and 20-minute time points. Subjects who drop out (for any reason) or take rescue medication will be considered non-responders unless they have already met the criteria to be considered responders.

- Onset of "Meaningful" Relief

  Onset of "meaningful" relief is defined as the elapsed time from dosing displayed on the stopwatch, and must be confirmed by either the pain intensity at the immediately following assessment being less than the baseline pain by at least 1 unit on the DPS or the pain relief score on the DPRS at the immediately following assessment being at least 1 ("A little"). If the confirmation is not achieved, then the stopwatch press will be considered unreliable and the subject will be censored, for

analysis purposes, at the time of the press. Any subject who drops out or takes rescue medication before onset is attained will be considered censored for analysis purposes. The censoring is at the end of the scheduled evaluation (120 minutes) if the dropout is due to lack of efficacy (LOE) or if rescue medication was taken; otherwise it is at the time of the dropout.

The onset times will be statistically compared between the groups, based upon all the subjects. In addition, the onset times based on just the responders in each of the two benzocaine groups will be summarized in order to provide estimates of how quickly benzocaine provides relief among those who attain it.

- Duration of Effect

Duration of effect is defined as the time difference between onset of effect and its offset. Onset of effect is the first time point at which two consecutive pain scores less severe than at baseline by at least 1 unit (on the DPS) are attained. Offset of effect is the first of the following events to occur after onset: time to drop out if the drop out is due to lack of efficacy, time of rescue medication, or the first time point following onset of effect at which two consecutive pain scores that are at least as severe as at baseline are attained. For example, suppose a subject does not take rescue medication and records pain scores on the DPS as follows:

Time point	0	5	10	15	20	25	30	40	50	60	70	80	90	100	110	120
Score	3	2	3	**2**	**2**	2	3	2	2	**3**	**3**	3	3	3	3	3

This subject's onset of effect would be 15 minutes and offset would be 60 minutes, and thus the duration of effect would be 45 minutes. (Note: the first recorded pain improvement is at 5 minutes, but the following assessment is equal to baseline, and thus 5 minutes does not qualify for the onset time. Likewise, the first recorded time at which the pain returns to baseline levels does not qualify as the offset time in this example).

When onset or offset of effect is not attained, duration will be assigned as follows:

a. Subjects who do not experience onset of effect, including those who drop out or take rescue medication, will be assigned a duration of 0 minutes unless they drop out due to reasons unrelated to efficacy, in which case they will not be included in this analysis.

b. If a subject experiences onset and completes the study without taking rescue medication, then the subject's duration will be considered censored

with a censor time of 120 minutes (the scheduled study duration) minus the onset time.

c. If a subject experiences onset but not offset and drops out due to reasons unrelated to efficacy, the subject's duration will be considered censored for this analysis with a censoring time equal to the dropout time minus the onset time.

The duration times will be statistically compared between the groups, based upon all the subjects. In addition, as with the onset times, the durations based on just the responders in the benzocaine groups will be summarized in order to provide estimates for how long benzocaine provides relief among those who attain it.

- Individual Time Point and Summary Pain Efficacy Scores

  - Pain Intensity Differences (PID): based on the 4-point dental pain scale ranging from 0 (none) to 3 (severe), is derived by subtracting the score at each post-dosing time point from the baseline score, so that a higher positive value is indicative of greater improvement. These scores will not be analyzed but will be utilized in deriving PRID scores, which will be analyzed.

  - Pain relief scores combined with pain intensity difference scores (PRID) will be calculated at each post-dosing time point by summing the PID score and the pain relief score.

  - SPRID, time-weighted (weighted by time since the prior scheduled assessment) sum of PRID scores, over 30, 60, 90 and 120 minutes will be calculated.

8.5 STATISTICAL MODELS

The analyses described below incorporate effects for investigational site and the design stratification of baseline pain. Indicators of last alcohol and analgesic usage will be included in the analyses if they are unbalanced across the treatment groups and they impact on efficacy. In this event, subjects will be classified as to whether the time of their last analgesic usage was less than 8 hours prior to dosing and also classified as to whether the time of their last alcohol intake was less than 12 hours prior to dosing.

The percentages of subjects classified as responders in each group will be analyzed by the Cochran-Mantel-Haenszel (CMH) test controlling for site and baseline DPS. In order to assess whether the treatment effects depend upon site or baseline DPS, the p-values of their

interactions with treatment will be computed using the pseudo-homogeneity test of Koch, et al.[2]

The distributions of the time to "meaningful" relief, duration of effect and time to dropping out due to lack of efficacy or taking of rescue medication will be estimated for each treatment group, based upon all subjects, by the Kaplan-Meier estimate. The Cox proportional hazards regression model[3], adjusting for site and baseline DPS, will be used to compare the distributions. Interactions of treatment with site and baseline DPS will be tested one at a time. If the treatment-by-site interaction is generally significant ($p \leq 0.10$), an additional analysis including this interaction term will be performed; however, the model without the treatment-by-site interaction will be considered primary. If the treatment-by-baseline DPS interaction is generally significant ($p \leq 0.10$), it will be retained in the final model, in which case, to assess the overall treatment effect, each level of baseline DPS will be weighted equally. Ninety-five percent confidence intervals for the median onset, duration, and dropout/rescue medication times will be derived by the method of Simon and Lee[4]. In addition, in each of the benzocaine groups 95% confidence intervals for the median onset and duration times will be derived based upon just the responders.

PRID and SPRID scores will be analyzed by Analysis of Variance (ANOVA), incorporating effects for treatment, site, and baseline DPS. In addition, the interactions of treatment with site and baseline DPS will be assessed in separate models, by adding each interaction term, one at a time, to the initial ANOVA model. If the treatment-by-site interaction is generally significant ($p \leq 0.10$) across variables, an additional analysis including this interaction term will be done; however, the model without the treatment-by-site interaction will be considered primary. If the treatment-by-baseline DPS interaction is generally significant ($p \leq 0.10$), it will be retained in the final model. If the parametric assumptions are grossly violated, these variables will be analyzed using CMH tests using modified ridit scores stratifying by site and baseline pain intensity.

Since previous studies have indicated that the baseline pain can markedly affect the efficacy of benzocaine, subgroup analyses of all the variables will be done within each level of baseline pain.

Summary statistics for the amount of product applied and the percentage of subjects who apply no more than 400 mg will be tabulated, along with a 95% confidence interval, computed based on a score test,[5] for the percentage.

8.6 PROTECTIONS FOR MULTIPLE COMPARISONS AND MULTIPLE ENDPOINTS

In order to present the full clinical picture, all pairwise comparisons will be presented. The study hypotheses of interest are:

- Benzocaine 20% is significantly ($p \leq 0.05$) more effective than placebo,
- Benzocaine 10% is significantly ($p \leq 0.05$) more effective than placebo,
- There is a dose-response between the 10% and 20% concentrations of benzocaine.

To control for the Type I error rate for the statistical tests of significance (the first two hypotheses), the second hypothesis will not be considered confirmed unless the tests of both the first and second hypotheses are significant ($p \leq 0.05$).

8.7 ESTABLISHMENT OF A DOSE-RESPONSE RELATIONSHIP

A dose-response will be considered established if a five-percentage-point increase in responders between the 10% and 20% benzocaine treatment groups is observed. Alternatively, since previous studies have suggested that the relative advantage of a 20% concentration of benzocaine to a 10% concentration is most evident among individuals suffering with severe toothache pain, a dose-response will be considered established if the five-percentage-point increase in responders between 10% and 20% benzocaine treatment groups is seen only within the subgroup of subjects presenting with severe toothache pain at baseline.

8.8 ANALYSIS OF POPULATIONS

The primary analysis of efficacy will use the intent-to-treat principle, in which all randomized subjects who receive study drug will be included. If appropriate, a secondary analysis of efficacy will exclude subjects who have significant protocol violations or take rescue medication prior to the 20-minute time point.

8.9 SAFETY ANALYSIS

The safety population will consist of all subjects who took study product and had follow up data.

Adverse event (AE) analyses will include all AEs which initially occurred, or worsened following treatment (*i.e.,* treatment emergent signs and symptoms, TESS). AEs will be summarized by the MedDRA preferred term and by system organ class and classified according to their intensity (mild, moderate, or severe) and relationship (definitely related, probably related, possibly related, probably not related or definitely not related) to study product. For the summary by severity, subjects who have multiple occurrences of the same AE will be classified according to the worst reported severity of the AE. Similarly, for the summary by relationship to the study product, the AE will be classified according to the "worst" relationship.

The incidence of TESS among treatment groups will be analyzed via the Fisher's exact test.

All non-TESS will be summarized according to the MedDRA preferred term.

9.0 STUDY ADMINISTRATION

9.1 INVESTIGATOR STUDY BINDER

The Sponsor will supply to the Principal Investigator an Investigator Study Binder that must be maintained at the study site, unless an alternative filing system is deemed appropriate by the CHPA Oral Discomfort Task Group representative.

Included in this binder will be tabbed sections for maintaining the following: study identification and study site staff signature list, monitoring visit record, protocol and amendments/administrative changes, Form FDA 1572, curricula vitae, Institutional Review Board documentation, sample informed consent form, product accountability forms, correspondence, subject screening record, master subject log, and when applicable, laboratory normal values and accreditation. This binder must be kept current and be available for review by representatives of the Sponsor.

9.2 SUBJECT IDENTIFICATION

For purposes of confidentiality and to maintain anonymity, subjects will be assigned identification numbers. Subjects will be numbered sequentially as they enter the study. Once subjects meet the entry criteria, they will be assigned a randomization number corresponding to study product. Subjects should be identified to the Sponsor only by their assigned number, initials, date of birth, and gender. The Principal Investigator will maintain a complete list of all subjects enrolled in the study with their current mailing address on the master subject log. This list is necessary should contact of subjects be required in the future.

9.3 CASE REPORT FORMS

Case report forms provided by CHPA Oral Discomfort Task Group will be used to document all subject data and will be typed or printed legibly in black or blue ink. Prior to submission to CHPA Oral Discomfort Task Group, the Principal Investigator will review all case report forms and sign where necessary. It is important that the case report forms be completed in a timely manner for each subject evaluation in order that the progress and results of the study may be closely followed by the Sponsor. Corrections to case report forms must not obscure the original entry; a single line through the original entry is sufficient. All corrections must be initialed and dated by the responsible individual.

Case report forms are to be completed and held for retrieval by a representative of the CHPA Oral Discomfort Task Group, unless otherwise directed. All study records must be retained in accordance with Section 9.10. A study site may use forms of their own design, following approval of the form by the CHPA Oral Discomfort Task Group, as source documents only.

9.4 MONITORING OF STUDY

The study will be monitored by the representatives of the CHPA Oral Discomfort Task Group. On-site visits will be made before the study begins, at regular intervals during the conduct of the study, and at the completion of the study. Communication by telephone, mail, and facsimile may also be used to supplement on-site visits.

A representative of the CHPA Oral Discomfort Task Group will inspect all case report forms and corresponding portions of the subject's original office and/or hospital records. These inspections are for the purpose of verifying adherence to the protocol and determining the

completeness and exactness of the data entered on the case report form and study product log.

As a part of monitoring and inspection of this study, the Principal Investigator agrees that the CHPA Oral Discomfort Task Group, its employees or representatives, Institutional Review Board or Independent Ethics Committee, as well as representatives of the Food and Drug Administration and other regulatory authorities will have the right to inspect and review pertinent medical records relating to this trial. In addition, informed consent documents signed by study participants will indicate approval to release their medical records for review while maintaining their confidentiality.

9.5 PROTOCOL MODIFICATIONS

As the study progresses, any necessary additions or changes to the protocol will be decided by mutual agreement of the Principal Investigator at each site and the Clinical/Medical Monitors. An amendment to this effect will be submitted first to the CHPA Oral Discomfort Task Group for review and approval and then to the Institutional Review Board at each site for review and approval prior to implementation. If the protocol change impacts the conduct of the study, the informed consent form will be amended, as appropriate. A protocol change to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the FDA and/or the reviewing Institutional Review Boards at each site are notified in accordance with 21 CFR 56.104(c). Otherwise, no deviations will be permitted.

9.6 DISCONTINUATION OF STUDY

The CHPA Oral Discomfort Task Group reserves the right to discontinue the study for administrative reasons at any time. The Principal Investigator will be reimbursed for reasonable expenses incurred if it is necessary to terminate the study. All study product and case report forms will then be returned to the Sponsor.

If the Principal Investigator discontinues the study prematurely, the Principal Investigator will return all study product and case report forms to the Sponsor and provide a written explanation as to why the study was ended.

9.7 DISCLOSURE OF DATA/PUBLICATION

All information obtained during the conduct of the study will be regarded as confidential. Agreement from the CHPA Oral Discomfort Task Group must be obtained prior to disclosing any information relative to the study.

Upon completion of the study, the CHPA Oral Discomfort Task Group may or may not decide to publish the results with the Principal Investigator in a recognized scientific journal or present the results (as a poster or oral presentation) at a meeting of a recognized scientific association. In order to safeguard against disclosure of confidential information, however, the CHPA Oral Discomfort Task Group requires that any manuscript and/or abstract receive its approval prior to submission. A draft manuscript must be reviewed by the CHPA Oral Discomfort Task Group 60 days prior to submission of the final version to the journal. Abstracts of presentations must be reviewed by the CHPA Oral Discomfort Task Group 30 days prior to submission. The CHPA Oral Discomfort Task Group assures the Principal Investigator that all manuscripts and abstracts will be reviewed promptly.

9.8 INFORMED CONSENT

Federal regulations require that written informed consent must be obtained for each subject prior to entry into the study. Informed consent means the knowing consent of an individual or his/her legal authorized representative, so situated so as to exercise free power of choice without undue inducement or constraint or coercion. The elements of information necessary for such consent include:

a. A statement that the study **involves research** and a fair explanation of the procedures to be followed and their purpose, including identification of any procedures which are experimental;

b. A description of **any discomforts**, **any risks** reasonably to be expected, and **any unforeseeable risks** to the subject or fetus (if applicable);

c. A description of **any benefits** reasonably to be expected;

d. An indication of the **approximate number of subjects** involved in the study;

e. A disclosure of **any appropriate alternative procedures or treatments** that might be advantageous for the subject, including examples;

f. A description of the **confidentiality** of subject's medical records and possible review by the CHPA Oral Discomfort Task Group and the FDA;

g. An explanation of **individual to contact** to answer any inquiries concerning the research, the subject's rights, any research-related injury, including appropriate personnel names and telephones numbers;

h. An explanation of **compensation or free medical treatment** available for any research-related injury;

i. An instruction that the subject is **free to withdraw consent** and to **discontinue participation** in the project or activity at any time without penalty or loss of benefits to which subject is otherwise entitled to the subject. A statement that participation is **voluntary**;

j. An indication of **any additional costs** to the subject that may result from participation in the study;

k. Assurance that if a **change in condition** places the subject at risk, the subject will be withdrawn from the study and appropriate therapy will be instituted. Any significant new findings relevant to the subject's participation will be provided to the subject. It is within the Principal Investigator's discretion to drop the subject from participation, including lack of cooperation.

In addition, the agreement entered into by the subject should include no exculpatory language by which the subject is made to waive, or appear to waive, any of his/her legal rights or to release the institution or its agents from liability or negligence. Written informed consent will be obtained in the manner and by use of forms usually employed by the Principal Investigator, and approved by the respective Institutional Review Board. A copy of the consent form will be provided to the subject and/or his/her parent or guardian.

Each Investigator will provide the CHPA Oral Discomfort Task Group with a copy of the consent form as approved by the respective Institutional Review Board.

Each Principal Investigator will ensure that this study is in full conformance with the principles of the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong, and South Africa).

9.9 INSTITUTIONAL REVIEW

Prior to initiating the study, the protocol and amendments, informed consent form, any advertisement, each Principal Investigator's and sub-investigators' curriculum vitae, and investigational product brochure (or package insert) must be reviewed and approved by a properly constituted Institutional Review Board (IRB) as required by federal regulations (21 CFR Part 56) and International Conference on Harmonization (ICH) Guidelines.

The names and affiliations of all members of the committee must be provided to the Principal Investigator and the CHPA Oral Discomfort Task Group. Each Institutional Review Board must provide a signed and dated statement that the protocol, informed consent form, and other pertinent documents, such as recruitment advertisements (in any medium), have been approved by the committee. If the study continues longer than one year, each site must obtain a re-approval from the respective Institutional Review Board on an annual basis. The respective Institutional Review Board must be informed of any changes in research activity including amendments to the protocol and/or informed consent form, advertisements, and serious adverse events.

At the conclusion of the study, each Principal Investigator must submit a summary of the study to the respective Institutional Review Board with a copy forwarded to the CHPA Oral Discomfort Task Group no later than 60 days after the study closeout visit.

9.10 RETENTION OF RECORDS

International Conference on Harmonization and U.S. federal regulations require that all study records be kept in the files of the Principal Investigator for two years after the investigation is completed and submitted to the FDA. The CHPA Oral Discomfort Task Group will notify the Principal Investigators of the above date.

If at any time the Principal Investigators are no longer able to maintain the required study records, or if any of the Principal Investigators relocates or delegates custody of the records to another, the CHPA Oral Discomfort Task Group must be notified in writing as soon as possible. In any case, the CHPA Oral Discomfort Task Group retains the right to reclaim all study records. If the CHPA Oral Discomfort Task Group reclaims the study records, the master subject log, which contains confidential information identifying and how to contact the study subjects, will be provided to the CHPA Oral Discomfort Task Group in a sealed envelope labeled "confidential."

The Investigator assumes the responsibility of retaining the following records:

a. Signed and dated protocol and amendments, written authorization to allow enrollment of potentially ineligible subjects or otherwise amend the protocol;

b. Signed FDA Form 1572 with curriculum vitae of the Principal Investigator and sub-investigators;

c. Records of receipt and disposition of all product supplies, including:

- dates and amounts received from the CHPA Oral Discomfort Task Group;
- lot numbers or other identification,
- date and quantity dispensed and returned for each subject,
- dates and amount returned to the CHPA Oral Discomfort Task Group;

d. Institutional Review Board approval, correspondence, interim reports, and final study summary;

e. Documented informed consent for each subject;

f. Completed case report forms and diaries (if applicable) for each subject including all source documents from which the case report forms were prepared;

g. Subject screening record indicating disposition of each subject and reason for exclusion when appropriate;

h. Master subject log indicating all subjects enrolled in the study with their current mailing address;

i. Detailed medical histories for each subject containing:

- medical history prior to enrollment with basic identifying information linking records to case report forms, results of all diagnoses made, therapy provided, any other data on subject's physical state,
- medical history during the study including documentation of enrollment, concomitant or concurrently administered therapy, observations on subject's condition during the study, any factors that might alter the effects of the test product, adverse event or laboratory abnormality reports and follow-up where appropriate;

j. Copies of tests and/or examinations results required by the protocol, including laboratory normal values and accreditation, if applicable;

k. Copies of interim and final reports issued to the Institutional Review Board of the CHPA Oral Discomfort Task Group;

l. Documentation of contacts between the CHPA Oral Discomfort Task Group and the Principal Investigator and/or other study site personnel, including all correspondence;

m. Copies of any reports on serious adverse events, death, or life-threatening symptoms;

n. Roster of all study personnel with their signatures and signed initials;

o. Monitoring visit record.

9.11 RESPONSIBILITIES OF INVESTIGATOR

In agreeing to conduct this study, each Principal Investigator assumes certain responsibilities mandated by federal regulations: an Investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan as defined by the protocol, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the Investigator's care; and for the control of the products under investigation. An Investigator will, in accordance with the appropriate federal regulations, obtain the informed consent of each human subject to whom the product is administered. The Investigator will retain all study documents as stipulated in Section 9.10. The Investigator certifies that he/she has not been disbarred by the FDA from conducting clinical trials. The Investigator will comply with the requirements outlined in 21 CFR 54, Financial Disclosure by Clinical Investigators.

9.12 FILING OF PROTOCOL WITH FDA

This protocol will be filed with the FDA for concurrence.

10.0 REFERENCES

1. Potter JL, Hillman JV. Benzocaine induced methemoglobinemia. 1979; J Am Coll Emerg Phys 8: (26) 22-27.

2. Koch GG, Carr GJ, Amara IA, Stokes ME, Uryniak TJ. Categorical data analysis. In Berry DA, ed. Statistical Methodology in the Pharmaceutical Sciences. New York: Marcel Dekker, 1990: 389-474.

3. Cox DR. Regression models and life-tables (with discussion). 1972; J Roy Stat Soc Series B 34:187-220.

4. Simon R, Lee YJ. Nonparametric confidence limits for survival probabilities and median survival time. 1982; Cancer Treatment Reports 66:37-42.

5. Agresti A, Coull BA. Approximate is better than exact for interval estimation of binomial proportions. 1998; The American Statistician 52: 119-126.

APPENDIX I

LABEL INSTRUCTIONS

Label Instructions

Note: This Drug Facts Label was intended to instruct study subjects in applying the medication. It is not presented as a proposed label for marketed products.

Drug Facts

Active ingredient **Purpose**

Uses temporarily relieves pain due to toothache

Warnings

Allergy alert: do not use this product if you have a history of allergy to local anesthetics such as procaine, butacaine, benzocaine or other "caine" anesthetics.

Do not use ■ more than directed ■ for more than 7 days unless told to do so by a dentist or doctor

Stop use and ask a doctor if ■ swelling, rash or fever develops ■ irritation, pain, or redness persists or worsens

Keep out of the reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions ■ do not use if tube tip is cut prior to opening ■ cut open tip of tube on score mark

Adults and children 2 years and older	■ place this amount  on your fingertip ■ spread medicine onto painful tooth and surrounding gum ■ use up to 4 times daily or as directed by a dentist or doctor
Children under 12 years	Should be supervised by an adult in the use of this product
Children under 2 years	Ask a dentist or doctor

Other information This preparation is intended only for temporary relief of toothache pain until a dentist can be consulted. Seek dental care as soon as possible to treat cause of toothache.

Inactive ingredients

Questions or comments?